Remarks

Claims 1-15 are pending, prior to entry of this Amendment. The Claims are currently restricted to Groups I and II defined in the restriction requirement of September 23, 2008, wherein substituent X has been restricted to O, S, S(=O), $S(=O)_2$, and presumably CH_2 (substituent $X=CH_2$ was not addressed in the restriction requirement and is assumed to still be pending). Group III, defined as $X=NR^a$, is currently withdrawn and recitations thereof have been cancelled herein.

By way of this Amendment, claims 1, 12, and 15 have been amended, and claims 10 and 11 have been canceled. No new matter has been added.

Claim Objections

Claim objections have been addressed by amendment. Additionally, the phrase "have a meaning of" has been removed from claim 1 to correct the grammar of the claim.

Claims Rejections under 35 USC 112, 1st Paragraph

Claims 1-15 are rejected under 35 USC 112, first paragraph, as being non-enabled for the solvates of a compound of formula (I). Recitation of solvates has been removed from the claims. Note, even though solvates are not specifically recited, the recitation of "a compound of formula I" encompasses solvates thereof since those solvates necessarily include the compound that is solvated.

Claims 1-15 are rejected under 35 USC 112, first paragraph, as non-enabled for treatment of conditions other than depression, bipolar disorder, addiction, anorexia, stroke, Alzheimer's disease, and Parkinson's disease. The claims have been amended to recite methods of treating only those conditions recognized by the Office as enabled by the specification (i.e. depression, bipolar disorder, addiction, and stroke). Further, the specification has been amended such that the definition of "treating", as recited in the claims, does not include prevention.

Claims Rejections under 35 USC 103(a)

Claims 1-15 are rejected under 35 USC 103(a) as being unpatentable over Mercep, et al. WO '890, when combined with King (Medicinal Chemistry, 1994, provided in IDS), further combined with Muller and Ackenheim (Progress in Neuropsychopharmacology and Biological Psychiatry, 1998), and still further combined with Tobinick '961.

Concerning the recited compounds, the Office argues that the difference between the claimed invention and that of Mercep '890 is that the claimed compounds have a furan ring instead of thiophene ring. The Office argues that King teaches that replacement of S with O in a ring is expected to produce compounds having similar biological activity (bioisosterism), and concludes that the claims are prima facie obvious over the reference compounds in view of King.

There is not sufficient motivation provided by King to motivate one of skill in the art to modify Mercep WO '890 in order to arrive at the recited compounds. The Office has improperly re-constructed Applicants' invention using the Mercep '890 reference and the generalized teachings of King.

When combining references, we are guided in part by KSR, which instructs that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP 2143.01(III). ("As is clear from cases such as Adams, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. [...] This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.") KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007).

Here, the Office has (i) picked one of many bioisosteric substitutions proposed by King, (ii) used the substitution to modify the compounds of Mercep

'890 to arrive at Applicants' compounds, and (iii) found Applicants' compounds obvious. This is done despite the fact that the King reference, itself, teaches that the result of such substitutions are unpredictable.

The King reference teaches that various bioisoteric substitutions may be made in search of drug optimization. King includes two tables (King, p.208, Tables 1 and 2) showing various isosteres. King does not indicated if such tables are exhaustive or merely samples of proposed substituents. King does, however, warn that isosteric and bioisosteric replacements are highly unpredictable

> "When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analyzing the result of such replacements. For example a simple CH2 to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pKa, metabolism, or hydrogen bonding capacity, all with **unpredictable effects upon biological activity**." (King, p. 209, emphasis added).

Concerning the type and location of the proposed substitution, it is important to realize that the Office picked one substitution from the various substitutions proposed by King and then applied that substitution to one of many particular locations on the Mercep '890 scaffold in order to construct Applicants' claimed compounds without any motivation (other than using Applicants' disclosure as a guide) to do so.

Even if King were to teach the specific substitution used by the Office, there is no suggestion as to which location of the Mercep '890 compound should be substituted. A large number of substitutions are taught by King, including the possibility of substituting any of the various -CH=CH- bonds of the compounds, without any suggestion to choose one substitution location over another. Further, even if Applicants' particular substituent were selected, it is not clear if

the substitution would act as a bioisostere. King only teaches that its proposed substitutions may function as bioisosteres. Further still, even if Applicants' substitution were selected and bioisosterism confirmed, it is unclear if one of skill in the art would be motivated to make the substitution.

A complete reading of King (Chapter 14) reveals that the reference stops well short of providing a reasonable expectation of success. Instead, the reference comments only generally on the function of bioisosteres:

> Bioisosteres [. . .] are substituents or groups that do not necessarily have the same size or volume, but have a similarity in chemical or physical properties which produce broadly similar biological properties. It is therefore unlikely that bioisosterism will produce marked increases in potency; however significant changes in selectivity, toxicity, and metabolic stability could be expected.
>
> (p. 207, 2nd full paragraph, emphasis added).

Thus, it is the Examiner, not the King reference, that alleges an expectation of success.

King simply provides that the claimed compounds may be bioisosteres of the reference compounds. Without hindsight, King provides no motivation to make the claimed compounds.

In the absence of any reasonable expectation of success, the Office has alleged that the King reference creates an "obvious to try" situation. Applicants assert that the "obvious to try" rejection is improper given: (i) the numerous possible substituents proposed by King; (ii) the numerous possible substitution sites on Applicants' molecule; and (iii) the lack of teaching or suggestion as to the proper substituent and substituted site to arrive at the claimed invention.

Concerning the claimed method of treatment, the Office must give weight to each of the recited limitations in a claim. See MPEP 2143.03. Here, the cited references deal generally with the subject of IL inhibition, but fail to teach or suggest, alone or in combination, each of the claim limitations. As an example, the claimed method (instant claim 1) of treating a disease, disorder or damage

associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter is not found in the references.

Mercep WO'890 only discloses the use of compounds to treat conditions associated with inhibition of TNFa. The disclosed conditions are predominantly related to inflammation and inflammatory disorders since TNFa inhibitors are recognized as an effective treatment for various inflammatory disorders, such as rheumatoid arthritis. Likewise, Tobinick '961 discloses a method of inhibiting interleukin (IL) for treating neurological conditions, and proposes that administration of IL-blocking might be effective in treatment of CNS disorders by reducing inflammation of neuronal tissue or neuromuscular junction. Muller and Ackenheil, like the others, disclose the inhibition of IL-1 and TNFa. Disclosure of the references is consistent with previously known uses of IL and TNFa inhibitors for treating inflammation. Thus, the cited references are consistent in their disclosure of TNFa inhibitors as valuable tools in treating inflammation.

Turning now to Applicants' invention, the Applicants have discovered, for the first time, that the recited tetracyclic compounds not only have binding affinity for TNFa receptors, but also have binding affinity for the o1 receptor and the 5-HT2A and 5-HT2C serotonin receptors. The o1, 5-HT2A, and 5-HT2C receptors are known to play a role in neurotransmission. Specifically, it has been observed that dopaminergic neurotransmission is regulated by 5-HT2A receptors, and it is thought that o1 receptor, at least in part, is an intracellular amplifier creating a supersensitized state for signal transduction in the biological system. See Background of instant application.

By binding to o1, 5-HT2A, and 5-HT2C receptors, the recited compounds are effective in treating CNS diseases, disorders, or damage caused by a disruption in the neurochemical equilibrium of a neurotransmitter. Assays are provided showing the binding affinity of the compounds, and mouse tests are provided to support the claims.

Turning back to the cited references, nothing in the references, even if combined, teaches or suggests the ability of the recited compounds to bind o1, 5-HT2A, or 5-HT2C receptors, or the use of the compounds to treat CNS

conditions caused by a disruption in the neurochemical equilibrium of a neurotransmitter. At most, the references suggest use of the known TNFa inhibitors to treat inflammation and inflammation-related disorders. But, treatment of TNFa-mediated, inflammation-based CNS conditions are not encompassed by the claims.

Applicants submit that, since the cited references fail to teach or suggest each of the claimed limitations, the pending rejection under 35 USC 103 is improper and should be withdrawn.

Claims 1-14 are rejected under 35 USC 103(a) as being unpatentable over Andres-Gil, et al. WO 99/19317, and claim 15 is rejected under 35 USC 103(a) as being unpatentable over Andres-Gil, et al. as applied to claims 1-14, and further in view of King (above).

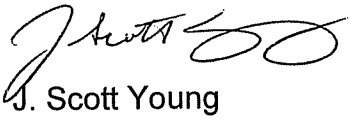
> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP 706.02(j)

The Andres-Gil reference discloses a compound having a tetrahydrofuran ring. The only support for the Office's obviousness rejection is to find Applicant's recited furan (unsaturated) compound over Andres-Gil's tetrahydrofuran (saturated) compound is the Examiner's own conclusion that "The compounds are so similar that one of ordinary skill would reasonably expect that they [the saturated and unsaturated rings] would behave similarly [...], in the absence of unexpected to results." This unsupported, conclusory statement is insufficient as a basis for an obviousness rejection. Indeed, even the cited King reference, which purports to described a laundry list of possible bioisosteres, doesn't go so far as to suggest that furan rings may be substituted for tetrahydrofuran rings. Thus, the Office has failed to provide a prima facie argument for obviousness with regard to the Andres-Gil reference, alone or in combination with King.

Conclusion

Applicants believe that no fees are due in connection with the filing of this paper other than those specifically authorized herewith. However, should any other fees be deemed necessary to effect the timely filing of this paper, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392. The Examiner is invited to contact the undersigned at (919) 483-8160, to discuss this case, if desired.

Respectfully submitted,



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